

A Phase II Study to Establish the Efficacy of Synthetic Human SecretiN in Human Acute Pancreatitis (SNAP) Study

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Research Coordination and Salary Support:
NIDDK - NIH
R21 Grant Application Pending – February 2017
(Final Funding Decision December 2017)

Study Drug and IND Holder:
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Study Product:

ChiRhoStim® (Synthetic Human Secretin for Injection)
NDA # 21-256
NDC # 67066-005-01
Cohort 1 Bolus Dose: 40 mcgIV q12hours
Cohort 2 Bolus Dose: 40 mcgIV q6hours
Cohort 3 Bolus Dose: 40 mcgIV q4hours

Protocol Number:

Version 1

IND Number:

56-821

Initial version: 2/27/2017
Amended: 11/27/2017
Amended: 11/30/2017
Amended: 3/13/2018
Amended: 06/06/2018

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List of Abbreviations

AE	Adverse Event(s)
BP	Blood Pressure
CBC	Complete Blood Count
CCK	Cholecystokinin
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator Gene
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
CRP	C-Reactive Protein
CT	Computed Tomography
e.g.	<i>Exempli Gratia</i> (for example)
ERCP	Endoscopic Retrograde Cholangiopancreatography
etc.	<i>Et cetera</i> (and so forth)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICU	Intensive Care Unit
IL	Interleukin
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
mcg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeters of Mercury
n	Number
O ₂ Sat	Oxygen Saturation
PE	Physical Examination
pH	Ion of Hydrogen
SAS®	Statistical Applications Software
USP	United States Pharmacopoeia
VAS	Visual Analog Scale (Score)
vs.	Versus
WSR	Westegren Sedimentation Rate

Study Summary

Title	A Phase II Study to Establish the Efficacy of Synthetic Human Secretin in Human Acute Pancreatitis (SNAP) Study
Short Title	Secretin for acute pancreatitis
Protocol Number	1
Phase	Phase II
Methodology	Randomized, dose escalation trial
Study Duration	Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study)
Study Center(s)	Multicenter – Dartmouth-Hitchcock Medical Center and Ohio State University
Objectives	<ol style="list-style-type: none"> 1) To perform a Phase II Pilot Study to explore the efficacy of intravenous synthetic human secretin as a pharmacologic adjunct to modulate the severity of human acute (non-obstructive) pancreatitis. 2) To explore the efficacy when escalating the frequency of daily intravenous synthetic human secretin dosing in the setting of human acute pancreatitis. 3) To evaluate the safety of intravenous synthetic human secretin in the acute pancreatitis population. 4) Use data from this phase II pilot study to appropriately design a definitive, prospective trial of human secretin in acute pancreatitis.
Number of Subjects	40 patients at two centers (20 patients at each center)
Diagnosis and Main Inclusion Criteria	<ol style="list-style-type: none"> 1. Patient is male or female ≥ 18 years of age 2. Patient voluntarily signed written, informed consent agreement. 3. If patient is female and not more than 1 year post-menopausal, or surgically sterile, must use medically accepted form of contraception or abstain from sexual activities during study. 4. Patient has non-obstructive acute pancreatitis via the 2012 Atlanta Classification.
Study Product, Dose, Route, Regimen	ChiRhoStim® 40 mcg IV Bolus q12hr (Cohort 1), q6hr (Cohort 2) and q4hr (Cohort 3) Mode of Administration: IV Bolus over 1 minute.
Duration of administration	40 mcg IV Bolus q 12hr for Cohort 1; 40 mcg IV Bolus q 6hr for Cohort 2 or 40 mcg IV Bolus q 4 hr for Cohort 3 x 3 days
Reference therapy	Standard of care in Cohort X (OBSERVATIONAL cohort)
Statistical Methodology	No power calculation is necessary for this study since it is a pilot study. The pilot study will be utilized to calculate the power of a large multicenter study.

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1. Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

The development of innovative diagnostic, preventive, and therapeutic approaches to pancreatitis has the potential to reduce the burden of this disease in both children and adults. The 2009 **National Commission on Digestive Diseases (NCDD)** recommended a series of research goals that focused on the most prevalent pancreatic disorders—acute and chronic pancreatitis and their sequelae.¹ ***This exploratory R21 grant proposal specifically addresses Research Goal 10.4: Develop and validate therapeutic interventions for the treatment and/or progression of pancreatitis and its complications.*** We anticipate that this exploratory study will demonstrate a promising signal that human intravenous secretin should be investigated further as a pharmacologic therapy to improve patient outcomes in acute pancreatitis.

Acute pancreatitis is a frequently devastating pancreatic inflammatory process that results in extensive morbidity, mortality, and hospitalization costs.² The incidence of acute pancreatitis has been increasing over the last decade with an overall mortality rate of 5%, although it may be as high as 30% in the most severe cases.³ It was the most common inpatient gastrointestinal diagnosis in 2009, totaling over 270,000 hospitalizations with estimated “inpatient costs” of over 2.5 billion dollars in the United States.⁴ **However, despite the significant impact to both patients and the healthcare system, there is no proven pharmacologic therapy that improves important clinical outcomes in acute pancreatitis.**

Table 3. Gastrointestinal and Hepatology Principal Discharge Diagnoses from Hospital Admissions, 2009

Most common principal discharge diagnoses									
Rank among GI dx	Rank among all dx	ICD-9-CM code(s)	Principal diagnosis name	Total No. discharges	% Change from 2000	Median LOS (days)	Total hospital days (in thousands)	Median costs (USD)	Aggregate cost (USD, in thousands)
1*	21	577.0	Acute pancreatitis	274,119	+30	4.0	1409	6096	2,599,686
2	41,76	574.0, 574.1	Cholelithiasis with cholecystitis*	226,216	-14	3.0	819	8322	2,208,531
3	27	562.11	Diverticulitis without hemorrhage	219,133	+41	4.0	1099	6077	2,115,989
4	29	540.9	Acute appendicitis	207,345	+22	1.0	362	6592	1,491,402
5	30	507.0	Aspiration pneumonia	188,930	+6	6.0	1475	9030	2,523,299
6	37	558.9	Noninfectious gastroenteritis/colitis	151,856	+36	2.0	462	4090	775,020
7	44	578.9	Gastrointestinal hemorrhage NOS	140,497	+22	3.0	612	8090	1,155,971
8	46	560.9	Intestinal obstruction NOS	134,431	+44	3.0	600	5098	1,018,437
9	47	278.01	Morbid obesity	132,448	+314	2.0	288	10,689	1,642,293
10	57	8.45	Clostridium difficile infection	110,553	+237	5.0	761	6774	1,119,213
11	73	560.81	Intestinal adhesions with obstruction	83,183	+23	7.0	736	11,853	1,453,238
12	94	8.8	Viral gastroenteritis	66,842	+29	2.0	181	3677	298,507
13	96	530.81	Esophageal reflux	65,634	-32	2.0	162	4366	386,229
14	100	562.12	Diverticulosis with hemorrhage	64,222	-6	3.0	291	5818	552,906

Peery et al. *Gastroenterology* 2012;143:1179-87.⁴

The pathophysiology of acute pancreatitis involves an inciting event – excessive alcohol use, transient obstruction of the ampulla of Vater via a biliary stone, excessive free fatty acid formation in toxic serum concentrations, for example – although the precursor mechanism of action that leads to acute pancreatitis remains unknown.^{5,6} **Following this acute inciting event, the exocrine pancreas inappropriately initiates the intra-acinar activation of trypsinogen to activated trypsin which is normally only activated after reaching the duodenum.**⁷ This inappropriate synthesis of activated intra-acinar trypsin results in the generation of large amounts of active trypsin within the pancreas, which then catalyzes the activation of more trypsin and other proteolytic enzymes such as chymotrypsin and elastase, with subsequent initiation of other enzyme cascades such as complement, kalikrein-kinin, coagulation and fibrinolysis.^{8,9}

As intra-acinar accumulation of activated enzymes exponentially increases, pancreatic autodigestion occurs, leading to the release of even more active enzymes from damaged cells.¹⁰ The release of pancreatic enzymes then stimulates leukocyte chemo-attraction, microcirculatory injury and subsequent granulocyte and macrophage activation causing the release of proinflammatory cytokines (tumor necrosis factor, interleukins 1, 6, and 8), arachidonic acid metabolites (prostaglandins, platelet-activating factor, and leukotrienes), proteolytic and lipolytic enzymes, and reactive oxygen metabolites, which overwhelm the scavenging capacity of endogenous antioxidant systems.^{3,11-13} These inflammatory mediators also interact with the pancreatic microcirculation to increase vascular permeability and induce thrombosis and hemorrhage.¹⁴ Finally, as a result of this inflammatory cascade, some patients will develop a sepsis-like syndrome featuring hypotension, capillary-leak syndrome, acute respiratory distress syndrome, and in some cases death.^{3,15}

Critical to the pathogenesis of acute pancreatitis is the inability of the pancreas to secrete these inappropriately activated intra-acinar pancreatic enzymes. The pancreas normally secretes inactivated trypsinogen into the duodenum via a cAMP mediated process within the pancreatic ductal cell that is under the control of the secretory hormone secretin¹⁶ Discovered over 100 years ago, secretin is a gastrointestinal hormone produced by the S-cells of the proximal small intestine in response to a meal and acts on the pancreatic ductal epithelial cells to stimulate the production of bicarbonate-rich fluid (pH 8.5).¹⁷ **The release of bicarbonate rich fluid into the pancreatic duct from the ductal cells is an important mechanism to protect against pancreatitis by two distinct mechanisms:**

1. **“Flushing” activated enzymes out of the pancreas and into the duodenum thereby preventing accumulation of activated enzymes within the pancreatic acinus**
2. **Directly alkalinizing the acinar cells, which limits intra-acinar cell damage by improving trafficking of inappropriately activated intra-acinar enzymes along the apical membrane.**¹⁸⁻²⁰

Patients with a defect in their ability to generate bicarbonate-rich fluid – i.e. in some gene mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene – develop acinar cell injury both from accumulation of activated intra-acinar enzymes and deficient trafficking of activated enzymes out of the acinar cell.^{21,22} Data from a study evaluating CFTR knock-out mice demonstrated that when luminal pH is corrected back to an alkaline environment, the membrane trafficking defect within the acinar cell reverses.²³ Acids within the lumen of the pancreatic acinus have also been implicated in the disruption of intracellular junctional links which has been postulated to involve the initiation of pancreatitis.^{24,25} Thus, a primary role of the ductal cells is to neutralize the large amount of acid content secreted by the acinar cells as a means of limiting the ongoing activation of the prematurely activated intra-acinar enzymes.

Previous efforts to develop clinically effective pharmacologic therapies for acute pancreatitis have targeted the inflammatory response using anti-proteases such as gabexate mesilate, antagonists of platelet activating factor such as lexipafant, corticosteroids, anti-IL-10, and anti-TNF- α ; however, none of these therapies have shown clinical efficacy.²⁶ Furthermore, significant effort has been invested in both animal and human *in vitro* and *in vivo* studies to try and develop an effective therapy for reducing pancreatic secretion in acute pancreatitis. Randomized clinical trials, based on pre-clinical *in vivo* studies, however, have not demonstrated any benefit with somatostatin, octreotide, atropine, glucagon, and/or cimetidine.²⁷⁻²⁹ The lack of clinical benefit to *suppressing* pancreatic secretions in human trials of acute pancreatitis has driven interest in exploring the opposite hypothesis – i.e. **stimulating the pancreas to enhance secretion of watery, bicarbonate-rich (pH 8.5) pancreatic fluid in**

order to flush the pancreatic ducts of pancreatic enzymes thereby stopping the ongoing activation of intra-acinar trypsin via pH inhibition.

1.2 Investigational Agent

Fortunately, there is a means available to stimulate secretion from the pancreatic ductal cells using a pure synthetic human secretin that has the identical 27 amino acid peptide sequence as the biologic form. Synthetic secretin has several advantages over the biologic form, not the least of which is a potential for an unlimited supply of drug, biochemical purity, a more predictable pharmacologic response and nearly no potential for immunogenicity.¹⁶ The hypothesis on which this pilot study is based is that human secretin, given to patients with acute pancreatitis, will stimulate pancreatic ductal secretion of bicarbonate-rich pancreatic fluid, which would wash out the pancreatic ducts of pancreatic enzymes, halt the ongoing activation of trypsin via pH inhibition within the pancreatic acinus and improve pancreatic acinar cell function. Such an intervention, we believe, has the possibility of improving meaningful outcomes in human acute pancreatitis.

1.3 Preclinical Data

We have extensive experience with designing, executing, completing and reporting prospective, clinical research studies studying human pancreatitis. In addition, we are among the few investigators who have executed randomized trials in acute pancreatitis and have published multiple clinical studies using secretin specifically for the diagnosis and treatment of human acute and chronic pancreatitis.^{30,31} The proposed pilot study is based on our extensive experience with administration of secretin and several years of data suggesting efficacy of secretin to treat human pancreatitis.^{32,33}

Animal studies. Animal studies have demonstrated that exogenous secretin administration produces a positive effect on the release of pro-inflammatory cytokines in the well-known cerulein-induced acute pancreatitis model in the rat without causing harm. Utilizing light microscopy and electron microscopy, Renner *et al* showed marked cellular disorganization in the acini of animals treated with cerulein alone.³⁴ In contrast, there was a striking apical redirection of zymogen granules, lessening of acinar vacuolization, interstitial edema and preservation of parenchymal architecture in the acini of animals treated with secretin. They also reported that secretin partially restored pancreatic function in rats with cerulein-induced acute pancreatitis.³⁵ Niederau *et al* reported that exogenous secretin lowered serum amylase levels, and exhibited less histopathological changes in cerulein-induced acute pancreatitis.³⁶

From a safety perspective, Evander *et al* showed no harmful effects of repeated subcutaneous injections of secretin in a murine acute pancreatitis model using sodium taurocholate.³⁷ From these animal studies it appears that exogenous secretin administration does not cause damage or worsen the outcome of cerulein- or sodium taurocholate-induced acute pancreatitis. In fact, in the cerulein model, secretin administration appears to 1) not be harmful, 2) reduce pancreatic histopathology, and 3) re-establish pancreatic juice flow and evokes a partial restoration of protein output when compared to non-secretin treated rats.

1.4 Clinical Data to Date

Human studies. The only human model of acute pancreatitis that can be studied readily is pancreatitis induced by instrumentation of the main pancreatic duct at the time of retrograde pancreatogram injection, otherwise known as ERCP-induced acute pancreatitis. Jowell and

colleagues in a prospective, randomized double-blind, placebo controlled trial (n = 844) showed a beneficial effect of secretin at statistically reducing acute pancreatitis when administered at the time of the procedure.³⁸

We are currently performing a phase III study (NCT02160808) of 176 patients undergoing pancreatic resection in which 50% of patients are randomized to intra-operative secretin administration and the other 50% to placebo with the intervention designed to allow for intra-operative identification and repair of pancreatic duct leaks. At the mid-point analysis, there was no evidence of increased leak rates or the development of acute pancreatitis in the secretin arm strongly arguing for the drug's safety in this patient population (internal data).

Furthermore, recent studies demonstrating the benefit of early oral and enteral nutrition administration in acute pancreatitis – a challenge to the long-held belief that pancreatic rest is of paramount importance – support the hypothesis that enhancing pancreatic secretion is potentially beneficial, and certainly not harmful.^{39,40}

We performed a pilot study in 12 patients to explore whether intravenous synthetic human secretin improves refractory type B pain in patients with chronic pancreatitis in a phase II dose escalation trial.³¹ We found that in patients, especially women, with refractory type B pain from chronic pancreatitis, intravenous secretin administration demonstrated a trend toward improvement in self-reported pain and opiate use at 30 days after infusion. Importantly there was no development of significant adverse effects in any of the patients with pancreatitis who received intravenous secretin. See figure below.

1.5 Dose Rationale and Risk/Benefits

In addition to standard care, patients will be divided into 4 cohorts. Cohorts 1,2 and 3 will be treated with different doses of intravenous synthetic human secretin. Cohort X will not receive human secretin, but all datapoints and specimens will be collected.

Cohort X (n=10): no ChiRhoStim® administered. All observations

Cohort 1 (n=10): 40 mcgChiRhoStim® two times a day (40 mcg; q 12 hrs)

Cohort 2 (n=10): 40 mcgChiRhoStim® four times a day (40 mcg; q 6 hrs)

Cohort 3 (n=10): 40 mcgChiRhoStim® six times a day (40 mcg; q 4 hrs)

Note: t_{1/2} for synthetic human secretin is 45 minutes (no accumulation possible).

The patient cohorts will be entered into the study as follows: Cohort X; Cohort 1; Cohort 2; Cohort 3. 5 patients in each cohort will be evaluated at each center (for a total of n=10 at both centers for each cohort). Dosing will start within 24 hours of hospitalization with no further synthetic human secretin administration beyond Day 3. Patients will continue to be followed for 7 days or until discharge, whichever comes first. Any data recorded to that point would be included in an intent-to-treat analysis.

2. Study Objectives

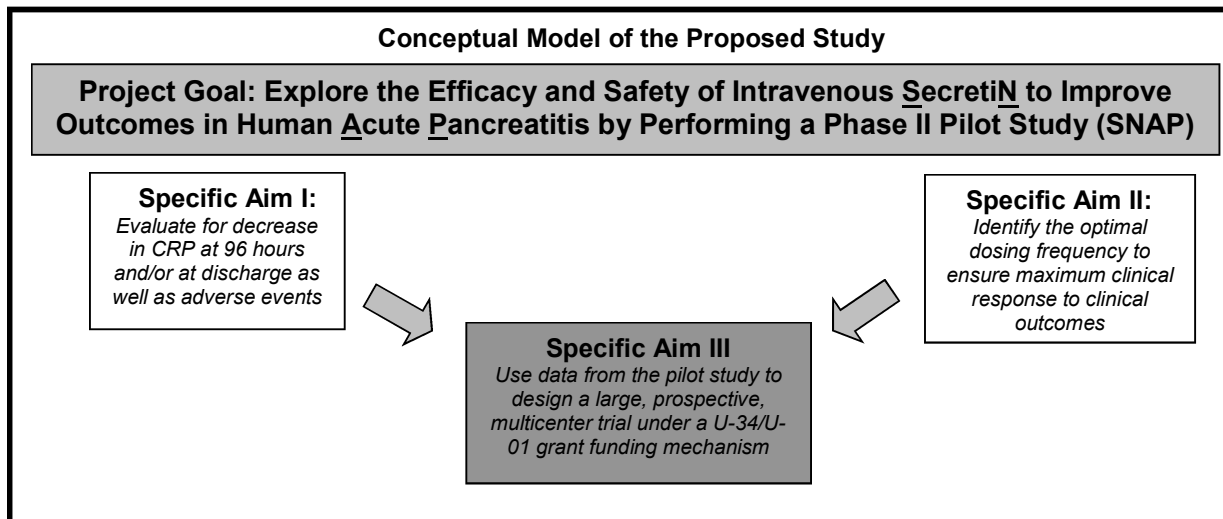
Aim 1: Perform a phase II pilot study utilizing intravenous human secretin to explore the efficacy of this pharmacologic adjunct to treat non-obstructive, acute pancreatitis. This pilot study will allow for the collection of important clinical and serologic endpoints to detect a possible signal that human secretin improves outcomes in acute pancreatitis. The study is not designed to be a definitive evaluation of treatment effect, and thus statistical significance for improvements in clinical and serologic outcomes is not expected. *An important aspect of the pilot study will be to confirm the safety of secretin administration previously observed in preclinical and human studies of acute pancreatitis.*

Aim 2: Explore the optimal dose frequency of intravenous human secretin to treat human acute pancreatitis. We chose three dose frequencies and a non-treatment arm for the study intervention. This dose is based on our dose escalation study of secretin to treat painful chronic pancreatitis. The dose frequency is based on the T1/2 of human secretin which is only 4 minutes. *A critically important component of this pilot is to determine if increased dosing frequency leads to improvement in clinical and serologic outcome measures.*

Aim 3: Use data from this phase II pilot study to design a prospective trial of human secretin in acute pancreatitis sponsored under an NIH U-34/U-01 grant mechanism. Data from this pilot study will be used to develop a multicenter study powered to definitively assess the clinical efficacy of this intervention. Cytokine expression data will allow further refinement of secondary outcomes, and provide initial insights into the potential mechanisms of action of secretin in this clinical setting. Dose frequency data will allow for design of properly randomized and dosed cohorts. *Finally, completion of the pilot will demonstrate study feasibility using this drug in this patient population.*

3. Study Design

3.1 General Design



Study Design: This is a prospective, phase II exploratory pilot study using different dose frequencies of intravenous human secretin in patients with non-obstructive, interstitial acute pancreatitis

Study Site

Principle Site: Dartmouth-Hitchcock Medical Center (Lebanon, NH) - Dr. Timothy Gardner, MD MS

Secondary Site: The Ohio State University (Columbus, OH) - Dr. Darwin Conwell, MD, MS

Study Population: 40 patients presenting to the emergency room within 24 hours of symptoms with non-obstructive, interstitial acute pancreatitis at Dartmouth-Hitchcock Medical Center (20 patients – 5 in each cohort) and Ohio State University (20 patients – 5 in each cohort).

Standard of Care Therapy: All enrolled patients will receive standard of care therapy in regard to fluid resuscitation, pain control, CT scan or ultrasound imaging and nutritional support

Intervention: In addition to standard of care, patients will be divided into 4 cohorts of 10 patients. Cohorts 1, 2 and 3 will receive different doses of intravenous synthetic human secretin. Cohort X will not receive drug.

Cohort X (n=10): NO human secretin administered (observational)

Cohort 1 (n=10): 40 mcg human secretin two times a day (40 mcg; q 12 hrs)

Cohort 2 (n=10): 40 mcg human secretin four times a day (40 mcg; q 6 hrs)

Cohort 3 (n=10): 40 mcg human secretin six times a day (40 mcg; q 4 hrs)

Dosing will start within 24 hours of hospitalization with no further secretin administration beyond Day 3. Patients will continue to be followed until discharge.

3.2 Primary Study Endpoints

1. Decrease in serum C-reactive protein (CRP) level by 50% within 96 hours and/or at discharge compared with CRP level at admission to determine optimal frequency of dosing.

3.3 Secondary Study Endpoints

1. Serum measurements of pro- and anti-inflammatory cytokines including sCD40L, EGF, Eotaxin/CCL11, FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN- α 2, IFN- γ , IL-1 α , IL-1 β , IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1 α , MIP-1 β , PDGF-AA, PDGF-AB/BB, RANTES, TGF- α ,

TNF- α , TNF- β , VEGF, HSP 27, HSP 60, HSP 70, HSP 90 at time of study enrollment, days of secretin administration, 96 hours and at discharge

2. Clinically relevant outcome measures including hemoconcentration (fall in blood urea nitrogen and hematocrit from admission), decrease in patient admission pain scores (visual analogue scale), decrease in systemic inflammatory response, and tolerance of oral nutrition
3. Calculation of the Dynamic Acute Pancreatitis Score - organ failure, systemic inflammatory response syndrome, abdominal pain, requirement for opiates and ability to tolerate oral intake.
4. Length of hospitalization, need for intensive care unit transfer, mortality, need for surgical, endoscopic or percutaneous intervention
5. Development of pancreatic necrosis and/or persistent organ failure
6. Adverse events and 30 day readmission rate

3.4 Primary Safety Endpoints

See above in Section 3.3 in regards to adverse events

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Patient is male or female ≥ 18 years of age
2. Patient voluntarily signed written, informed consent agreement.
3. If patient is female and not more than 1 year post-menopausal, or surgically sterile, must use medically accepted form of contraception or abstain from sexual activities during study
4. Patient has acute pancreatitis as defined by the Atlanta Classification of 2012
5. No evidence of obstructive pancreatitis on available cross-sectional imaging

4.2 Exclusion Criteria

1. Pancreatitis with duct obstruction or severe acute pancreatitis defined by Atlanta Classification
2. Pregnant woman, nursing mothers, or women of childbearing potential not on birth control
3. Known adverse reaction to human secretin

4.3 Subject Recruitment and Screening

Subjects will be those admitted to Dartmouth-Hitchcock Medical Center and/or the Ohio State University Hospital with acute pancreatitis within 24 hours of admission. Subjects will be identified by daily admission records. All subjects will be those admitted not in transfer.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients will be withdrawn from the study and not replaced for the following reasons:

- 1) Voluntary withdraws-any patient may remove himself from the study at any time without prejudice to his medical care. They will be analyzed in the "Intent to Treat" analysis.
- 2) Excessive toxicity felt secondary to synthetic human secretin necessitating halting of administration prior to full dose, such as:
 - a) Life threatening anaphylactic reaction, or
 - b) Any other life threatening reaction felt secondary to the treatment that results in grade 4 toxicity by CTCAE
- 3) Patient develops the need for ICU care.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. This should not be difficult for this study as patients will all be inpatients at both Dartmouth-Hitchcock Medical Center and/or the Ohio State University Medical Center.

4.5 Subject Randomization/Allocation

Patients will be assigned to each of the four groups (three drug doses and observation) in block groups of five – i.e. five patients will be assigned to the Cohort X, five patients will be assigned to the Cohort 1, then five to Cohort two, then five to Cohort 3 at each center. Once 20 patients have been assigned and data collected, the formal interim analysis will be performed. The process will continue in the same manner for the remaining 20 patients until study completion at Ohio State. Only 20 patients will be enrolled at each center. See 5.2 below

Study Drug

5.1 Description

Synthetic human secretin will be administered through an intravenous line. ChiRhoStim® will be reconstituted according to the package insert. The contents of each vial (16 mcg) will be reconstituted with 8 mL of sterile physiologic saline (0.9%) USP and then administered over 1 minute.

5.2 Treatment Regimen

The study is not blinded and does not require any randomization codes. Ten patients each will receive one of three treatments for Days 1, 2, and 3:

1. No secretin – standard of care and observation (Cohort X)
2. 40 mcg IV Bolus every 12 hours (Cohort 1)
3. 40 mcg IV Bolus every 6 hours (Cohort 2)
4. 40 mcg IV Bolus every 4 hours (Cohort 3)

½ of Cohort X (5 patients) will be completed first, then ½ of Cohort 1 (5 patients) will be completed, followed by ½ of Cohort 2, followed by Cohort ½ of Cohort 3. A Cohort X in 10 patients will not receive any synthetic human secretin but will have all observation and data as was obtained for the three synthetic human secretin treatment groups. Cohort X represents the standard of care of the institution without synthetic human secretin treatment. At the conclusion of 20 patients enrolled – five patients from each group – an interim analysis will be performed. If the interim analysis is acceptable, five more patients from each cohort will be enrolled.

Guidelines for Off Protocol Use of Synthetic Human Secretin

Synthetic human secretin will not be used for any off protocol use if the patients are enrolled in the current study.

Bolus Termination

IV bolus of the drug will be halted for any of the following reasons:

- 1) Any life-threatening toxicity.
- 2) Any anaphylactic reaction to any medication during the procedure.
- 3) Significant hypotension (systolic BP less than 90 mmHg) that does not correct with intravenous fluids.

5.3 Method for Assigning Subjects to Treatment Groups

See sections 4.6 and 5.2 above.

5.4 Preparation and Administration of Study Drug

The drug will be supplied by the investigational pharmacy or delegate. The drug will be received in its unconstituted form. Authorized and delegated staff will then reconstitute the medication and administer intravenously at the bedside per standard.

5.5 Subject Compliance Monitoring

All study drug will be given by the investigating physician or authorized and delegated study staff while the patient is in a hospitalized monitored setting. Thus, issues of compliance should be easily identified and addressed.

5.6 Prior and Concomitant Therapy

The patient will receive all standard of care therapies as per usual treatment for acute pancreatitis including intravenous fluids, analgesics and nutritional support.

5.7 Packaging

The drug will be given per bolus injection in an unlabeled syringe large enough to accommodate the fully prepared dose. Study drug will be stored under locked conditions, allowing only Authorized staff access to the study drug.

5.8 Blinding of Study Drug

There is no blinding component to this study.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The study drug will be sent directly from ChiRhoClin, Inc. to the Dartmouth Investigational Pharmacy. Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.9.2 Storage

The drug will be kept in the Dartmouth Investigational Pharmacy and stored in the standard fashion at -20 degrees Celsius. The drug is stable at controlled room temperature for 6 months. This will allow for sufficient supply to be stored under controlled (locked) room temperature conditions for dispensing outside of Investigational Pharmacy hours. Investigational Pharmacy will continue drug accountability recording and temperature monitoring in the controlled room temperature conditions.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team. The drug will be kept by the Dartmouth Investigational Pharmacy.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 PRE-TREATMENT EVALUATION – See Attachment A

Evaluations

- 1) Inclusion/Exclusion Criteria
- 2) History
- 3) Medication Review
- 4) Standard of Care CT/Ultrasound Review
- 5) Physical Examination
- 6) Standard of Care Laboratory Values
- 7) Research Specimen Collection

6.2 TREATMENT PLAN

Administration of Study Drug

Forty (40) patients are planned for this pilot study – 20 at each center. Synthetic human secretin will be administered through an intravenous line. ChiRhoStim® will be reconstituted according to the package insert. The contents of each vial (16 mcg) will be reconstituted with 8 mL of sterile physiologic saline (0.9%) USP. The total dose is given over 1 minute.

Guidelines for Off Protocol Use of Synthetic Human Secretin

Synthetic secretin will not be allowed for any off-protocol use in any patient enrolled in the current study.

Bolus Termination

IV bolus of the drug will be halted for any of the following reasons:

- 1) Any life-threatening toxicity.
- 2) Any anaphylactic reaction to any medication during the procedure.
- 3) Significant hypotension (systolic BP less than 90 mmHg) that does not correct with intravenous fluids.

Treatment Assignments

The study is not blinded and does not require any randomization codes. Ten patients each will receive one of three treatments for Days 1, 2, and 3:

No secretin – standard of care and observation (Cohort X)

40 mcg IV Bolus every 12 hours (Cohort 1)

40 mcg IV Bolus every 6 hours (Cohort 2)

40 mcg IV Bolus every 4 hours (Cohort 3)

A Cohort X of 10 patients will not receive any synthetic human secretin (observation) but will have all observation and data as was obtained for the three synthetic human secretin treatment groups.

6.3 INTRA AND POST-TREATMENT EVALUATION – See Attachment A

Evaluation during Study Drug Administration

- 1) Administration of study drug will be recorded.
- 2) Vital signs will be recorded pre and post dose.

6.4 STUDY ENDPOINTS

Study Endpoints

The change in biochemical parameters that represent local and systemic effects of acute pancreatitis will be monitored from Day 1 through Day 7, including:

changes from baseline values of hemoconcentration (fall in hematocrit and BUN), visual analogue scale pain scores, SIRS score and tolerance of oral nutrition.

Monitoring of vital signs per standard of care and adverse events will be done throughout the study - **See Attachment A**

Abdominal pain is a cardinal symptom of pancreatitis and will be monitored daily in morning and evening (visual analog scale 0-10) and treated based on standard practice guidelines.

Vital signs will be recorded at baseline prior to administration of study medication (synthetic human secretin) and throughout the study period per standard of care.

The following adverse events will be monitored throughout the study: any event resulting in study drug termination, significant change in pre and post dose vital signs (Heart Rate change 30bpm or greater) or Blood Pressure (20 point change or greater)) Infection, Organ Failure, and any event resulting in transfer to the ICU or Death.

Calculation of the Dynamic Acute Pancreatitis Score - organ failure, systemic inflammatory response syndrome, abdominal pain, requirement for opiates and ability to tolerate oral intake. Total opiate use will be expressed in morphine equivalents.

6.5 STANDARD OF CARE

Standard of care therapy for acute pancreatitis including fluid resuscitation, analgesia and nutritional therapy will be followed for all study participants. The only deviation from standard of care in this study will be the delivery of the Secretin bolus (depending on the randomization assignment). In addition, patients will have a tube of blood collected at standard endpoints at time of study enrollment, days of secretin administration, 96 hours and at discharge

7 Statistical Plan

7.1 Sample Size Determination

This pilot study does not require a power calculation. This pilot study is intended to collect, evaluate and assess the efficacy of administering human secretin to patients with acute pancreatitis.

7.2 Statistical Methods

The data obtained from the pilot study will be used to calculate the power and cohort dosing for a large multicenter study under the guidance of the Biometrics Group at Rutgers University. Planned subsequent analysis will evaluate C-reactive protein using an area under the curve technique for the first 96 hours and ANCOVA-type linear model approach for each outcome variable with attempt at log-transformation for skewed or outlying variables.

7.3 Subject Population(s) for Analysis

The statistical analysis for this study will use an all-treated population – i.e. any subject randomized into the study that received at least one dose of study drug.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

For the purposes of this study the following are the only events that will be collected and recorded:

- Any event resulting in the termination of study treatment
- Significant change in pre and post dose vital signs
 - o Change in blood pressure greater than 20 points
 - o Change in heart rate greater than 30 bpm
- Infection
- Organ failure
- Any event resulting in transfer to the ICU or Death

All specified adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
 - unexpected, and
 - serious or involve risks to subjects or others
- (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- | | |
|------------------------------|------------------------------------------------------------------------------------|
| • Study identifier | • Current status |
| • Study Center | • Whether study treatment was discontinued |
| • Subject number | • The reason why the event is classified as serious |
| • A description of the event | • Investigator assessment of the association between the event and study treatment |
| • Date of onset | |

8.3.1 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the study sponsor and IND holder by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Edward Purich, PhD

4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129
301-476-8388
301-476-9529 FAX

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 Investigator reporting: notifying the Dartmouth IRB

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth College IRB (CPHS) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Dartmouth IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Any AE related to the research procedures at Ohio State must be reported to the Dartmouth IRB (CPHS).

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB using the form: “Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

Reporting Deaths: more rapid reporting requirements

Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Dartmouth IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Dartmouth IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:

For clinical drug trials, the following events are also reportable to the Dartmouth IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
 - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
 - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
 - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.3.3 Investigator reporting: Notifying another IRB

Investigators who are not Dartmouth faculty or affiliated with a Dartmouth research site are responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

8.3.4 Sponsor reporting: Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***

Any study event that is:

- associated with the use of the study drug
- unexpected,
- fatal or life-threatening, and

- ***Within 15 calendar days***

Any study event that is:

- associated with the use of the study drug,
- unexpected, and
- serious, but not fatal or life-threatening
- or–
- a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Any finding from tests in laboratory animals that:

- suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements

Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

8.3.5 Sponsor reporting: Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

8.4 Unblinding Procedures

Neither medical personnel nor investigators will be blinded in this study.

8.5 Stopping Rules

The study will be stopped if after review of each completed cohort at each center (n=5) of patients who have receiving study drug (Cohorts 1,2, or 3) there is an increase in the number of adverse events or worsening of important clinical outcomes (length of stay, organ failure, necrosis, CRP level, dynamic acute pancreatitis score) compared with Cohort X (observational cohort). Increase in adverse events and/or worsening of important clinical outcomes will be defined as follows:

Compared to baseline (Cohort X) in 2/5 (40% of patients) at either center, patients in Cohorts 1, 2, or 3 develop:

- A change in CRP level from admission at 3 days and/or discharge that exceeds 50%
- Persistent organ failure at 3 days as defined by the dynamic acute pancreatitis score

- Need for intensive care unit transfer
- An increase in the dynamic acute pancreatitis score from admission at 3 days and/or discharge that exceeds 50%
- Any other life threatening reaction felt secondary to the treatment that results in grade 4 toxicity by CTCAE

At the conclusion of each cohort enrolled receiving study drug (n=5) interim analysis will be performed comparing that completed cohort with cohort X. Also at the time of interim analysis of all three cohorts combined – after five patients in each of the three treatment cohorts and after 20 patients enrolled (five from each cohort including cohort X) – if there is a signal toward harm in the above outcome measures, the study will be stopped.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site – Dr. Timothy Gardner at Dartmouth and Dr. Darwin Conwell (Chairman of the Section of Gastroenterology) at Ohio State. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

This trial will employ a data safety monitoring plan to provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data.

- a. Data Safety Monitoring Board (DSMB)
A data safety monitoring board will be established to provide oversight to both centers at Dartmouth-Hitchcock Medical and The Ohio State University Wexner Medical Center. The DSMB will be chaired by Dr. Kerrington Smith, MD (Section Chief, Surgical Oncology, Dartmouth Hitchcock Medical Center) and will have the following two members - Dr. Phil Hart, MD (Assistant Professor; Director, Section of Pancreatic Disorders; Division of Gastroenterology, Hepatology, and Nutrition, Ohio State University) and Dr. Stuart Gordon, MD (Professor, Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center).
- b. The DSMB will meet via telephone prior to the initiation of the study to introduce themselves and make sure all of the current study protocols are in place.
- c. The DSMB will perform an interim analysis after enrollment of 5 subjects into each cohort, including Cohort X, combined from both centers. The DSMB will meet by telephone to discuss study outcomes, identify any adverse events, and propose modifications to the protocol if needed – this will serve as the interim analysis. The DSMB will stop the study based on the stopping rules (see 8.5 above). As this is a small pilot study, it is very unlikely that a significant benefit to the treatment will be seen after twenty patients. The DSMB will provide a written report of the interim analysis to the primary investigator, sponsor and funding agency following their meeting after 5 patients have been enrolled in each cohort at each center.
- d. The primary investigator and/or delegate will be responsible for providing a summary report of adverse events to the NIH funding IC, individual IRBs and to the DSMB.

- e. Following the complete enrollment of each of the four cohorts at each center, the chair of the DSMB will provide a written report of the research activities to date, with specific attention to safety and adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10. Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan in **Attachment B**. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and Dartmouth compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth compliance and quality assurance offices.

11. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See **Attachments C1 and C2** for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12. Study Finances

12.1 Funding Source

This study will be funded through a United States National Institutes of Health R21 (NIDDK) grant. This grant was submitted on February 26, 2017. The study drug and clinical monitoring will be provided for by ChiRhoClin, Inc. the drug IND holder.

If the R21 grant is unsuccessful, the study will be funded by ChiRhoClin, Inc. as indicated in the sponsor contract.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Dartmouth investigators will follow the Dartmouth conflict of interest policy.

13. Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the primary investigator and the research team – including the publication of a negative study, except as required by Federal, State, or local laws and/or regulations. However, any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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15. Attachments

Attachment A: Study Procedures

Attachment B: Study Monitoring Plan

Attachment C1: Patient Informed Consent – drug cohort

Attachment C2: Patient Informed Consent – observational cohort